Literature Update Immunology

Period: 1-30 April 2010

IBD

- **Once-daily dosing of delayed-release oral mesalamine** (400-mg tablet) is as effective as twice-daily dosing for **maintenance of remission of ulcerative colitis**
- Toward a **safer use** of **thiopurines** in **inflammatory bowel disease**
- **Correlation** between the **Crohn's disease activity** and **Harvey–Bradshaw indices** in assessing Crohn's disease severity
- **Infliximab as rescue medication for patients with severe ulcerative/indeterminate colitis refractory to tacrolimus**
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- **Adalimumab for cutaneous metastatic Crohn's disease**
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- Relationships between **inflammatory bowel disease** and **perinatal factors**: Both maternal and paternal disease are related to preterm birth of offspring
- Efficacy of **early treatment with infliximab in pediatric Crohn's** disease.
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- Cystic fibrosis and Crohn's disease: **Successful treatment and long term remission** with infliximab
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- Efficacy and **safety of infliximab as rescue therapy for ulcerative colitis** refractory to tacrolimus

Safety

- The **risk of infections** with **biologic therapies** for **rheumatoid arthritis**
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- **Erythema multiforme during anti–tumor necrosis factor treatment for plaque psoriasis**
- Heterophile interference accounts for method-specific **dsDNA antibodies** in patients receiving anti-TNF treatment
- Alfonso Massara, Luigi Cavazzini, Renato La Corte, and Francesco Trotta. **Comment on: Sarcoid-like granulomatosis in patients treated with tumour necrosis factor blockers: 10 cases** - Rheumatology 2010 49: 1019-1021. And the reply by Claire Immediato Daïen, Cédric Lukas, Bernard Combe, and Jacques Morel. Comment on: Sarcoid-like granulomatosis **in patients treated with tumour necrosis factor blockers: 10 cases: reply**. Rheumatology 2010 49: 1021-1022

- Infliximab safety profile and long-term applicability in inflammatory bowel disease: clinical experiences from the Eastern side of Europe
- **Adalimumab Level in Breast Milk** of a Nursing Mother
- **Efficacy and safety of biologicals against immune-mediated diseases**: do benefits outweigh risks?
- A **safety assessment of tumor necrosis factor** antagonists during **pregnancy**
- **Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab** in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study
- Onset of **Wegener's granulomatosis during therapy with golimumab** for rheumatoid arthritis: a rare adverse event?
- Infections requiring hospitalization in the **Abatacept clinical development program**: an epidemiological assessment.
- **Insulin resistance in rheumatoid arthritis**: the impact of the anti-TNF-alpha therapy.

IBD

Gastroenterology. 2010 Apr;138(4):1286-96, 1296.e1-3. Epub 2010 Jan 11.
Once-daily dosing of delayed-release oral mesalamine (400-mg tablet) is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis
Sandborn WJ, Korzenik J, Lashner B, Leighton JA, Mahadevan U, Marion JF, Safdi M, Sninsky CA, Patel RM, Friedenberg KA, Dunnmon P, Ramsey D, Kane S.

BACKGROUND & AIMS: The practice of dosing mesalamines in divided doses for the treatment of ulcerative colitis (UC) began with sulfasalazine and was driven by sulfapyridine toxicity. This convention and the assumption that dosing multiple times a day is necessary to treat UC had not been challenged until recently. This study was conducted to determine the efficacy and safety of once-daily dosing of delayed-release mesalamine (Asacol 400-mg tablets) compared with twice-daily dosing for maintaining remission in UC patients. METHODS: A multicenter, randomized, investigator-blinded, 12-month, active-control trial was conducted to assess the noninferiority of delayed-release mesalamine 1.6-2.4 g/day administered once daily compared with twice daily in patients with mild-to-moderate UC currently in clinical remission. The primary end point was maintenance of clinical remission at month 6. RESULTS: A total of 1023 patients were randomized and dosed. The primary objective of noninferiority was met. At month 6, 90.5% of patients receiving once-daily dosing had maintained clinical remission, compared with 91.8% of patients receiving twice-daily dosing (95% confidence interval for twice daily - once daily, -2.3 to 4.9). At month 12, 85.4% of patients receiving once-daily dosing had maintained clinical remission, compared with 85.4% of patients receiving twice-daily dosing (95% confidence interval for twice daily - once daily, -4.6 to 4.7). Both regimens had low rates of withdrawals as a result of adverse events and serious adverse events. CONCLUSIONS: Once-daily dosing of delayed-release mesalamine at doses of 1.6-2.4 g/day was shown to be as effective as twice-daily dosing for maintenance of clinical remission in patients with UC.

Gastroenterology. 2010 Apr;138(4):1618-20. Epub 2010 Feb 21.
Toward a safer use of thiopurines in inflammatory bowel disease
Ricart E, Panés J.

No abstract available

Clin Gastroenterol Hepatol. 2010 Apr;8(4):357-63. Epub 2010 Jan 21.
Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity
Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P.

BACKGROUND & AIMS: Clinical trials of Crohn's disease generally use the Crohn's Disease Activity Index to assess disease activity; these calculations are complex, time-consuming, and impracticable. We investigated whether a simpler tool, the Harvey-Bradshaw Index, was equally effective in assessing disease severity. METHODS: Crohn's Disease Activity and Harvey-Bradshaw Index scores were collected from 2 large multicenter Crohn's disease studies. The PEGylated antibody fragment evaluation in Crohn's disease: safety and efficacy (PRECiSE) 1 and 2 trials assessed efficacy and tolerability of certolizumab pegol (PEGylated, humanized, Fab' fragment of an antitumor necrosis factor alpha antibody). PRECiSE 1 and 2 data were analyzed to determine if results from the Crohn's Disease Activity Index correlated with those from the Harvey-Bradshaw Index criteria for defining response and remission. RESULTS: Analysis of almost 1000 data pairs showed a positive correlation between scores. The correlation between the indices for pooled data from PRECiSE 1 and PRECiSE 2 was 0.800 (Spearman correlation coefficient). The correlations between indices for the PRECiSE 1 or PRECiSE 2 were 20.698 and 0.716, respectively (Kronecker product variance). A 3-point change in the Harvey-Bradshaw Index score corresponded to a 100-point change in the Crohn's Disease Activity Index (clinical response); scores < or =4 points corresponded to a Crohn's Disease Activity Index score < or =150 points (clinical remission). CONCLUSIONS: Results from the Crohn's Disease Activity Index correlate with those from the Harvey-Bradshaw Index; use of the Harvey-Bradshaw Index might permit simpler Crohn's disease activity assessment in long-term clinical trials, and facilitate standardized disease activity measurements and cross-center comparisons.

Aliment Pharmacol Ther. 2010 Feb 18. [Epub ahead of print]
Infliximab as rescue medication for patients with severe ulcerative/indeterminate colitis refractory to tacrolimus
Herrlinger KR, Barthel DN, Schmidt KJ, Büning J, Barthel CS, Wehkamp J, Stange EF, Fellermann K.

SUMMARY Background: The calcineurin inhibitor tacrolimus and the anti-TNF-antibody infliximab are established options in steroid refractory ulcerative colitis (UC). The aim of this study was to determine the efficacy of infliximab as rescue medication in patients failing to respond to tacrolimus. Aim: To evaluate the efficacy of infliximab-salvage therapy in patients with refractory ulcerative colitis failing to respond to tacrolimus Methods: Twenty-four patients were enrolled in this evaluation. Reasons for tacrolimus therapy were steroid-refractory disease in 19 patients and steroid dependency in 5 patients. All patients receiving infliximab had tacrolimus refractory active disease (Lichtiger score >10) and were treated with 5mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter if tolerated. Results: Six of 24 patients (25%) achieved remission following infliximab infusion and 4/24 (17%) had an initial response only but underwent proctocolectomy later due to loss of response (3) or development of a delayed hypersensitivity reaction (1). Fourteen patients (58%) completely failed to respond with 10 undergoing colectomy. Eight patients experienced side effects under infliximab including two infectious complications (herpes zoster and herpes pneumonia). Conclusions: Infliximab offers a therapeutic option as rescue therapy in about a quarter of patients with active UC after failing to respond to tacrolimus. This benefit has to be weighed against the risks of infectious complications.

Int Rev Immunol 2010;29(1):4-37.
Mechanisms and efficacy of immunobiologic therapies for inflammatory bowel diseases.
Ghosh N, Chaki R, Mandal V, Lin GD, Mandal SC.

Current advances in understanding of the pathogenesis of inflammatory bowel disease have encouraged the development of many new therapies targeted at specific and non-specific mediators of the inflammatory bowel disease inflammatory pathway. Crohn's disease and ulcerative colitis, two common inflammatory bowel diseases likely result from interaction of multiple genetic and environmental risk and protective factors, deregulation of mucosal immunity in gut and breakdown of delicate balance of proinflammatory and anti-inflammatory cytokines. Immunobiologic agents targeted against TNF, leukocyte adhesion, Th1 polarization, T cell activation, nuclear factor-kappaB (NF-kappaB), and others are being assessed and will open exciting perspectives on development of therapies for inflammatory bowel disease.

Dig Dis Sci. 2010 Apr;55(4):1066-78. Epub 2009 Jun 10.
Significant differences between Crohn's disease and ulcerative colitis regarding the impact of body mass index and initial disease activity on responsiveness to azathioprine: results from a European multicenter study in 1,176 patients
Holtmann MH, Krummenauer F, Claas C, Kremeyer K, Lorenz D, Rainer O, Vogel I, Böcker U, Böhm S, Büning C, Duchmann R, Gerken G, Herfarth H, Lügering N, Kruis W, Reinshagen M, Schmidt J, Stallmach A, Stein J, Sturm A, Galle PR, Hommes DW, D'Haens G, Rutgeerts P, Neurath MF.

In a survey comprising 1,176 patients with inflammatory bowel disease (IBD) we recently showed that azathioprine (AZA) beyond 4 years is beneficial in ulcerative colitis (UC) patients and in a subset of Crohn's disease (CD) patients. Here, we show for the first time that azathioprine responsiveness depends on body mass index (BMI). The relationship is reciprocal in UC and CD, with a better outcome in UC patients with a BMI<25 and in CD patients with a BMI>25. These observations are particularly interesting considering the evolving concept of a relationship between fatty metabolism and immune regulation. Additionally, we show that CD patients, but not UC patients, respond better to AZA when it is started in clinical remission. This observation may support data favouring a "hit hard and early" regime in CD. Finally, we were able to demonstrate a decrease in the incidence of CD-related complications requiring surgery through treatment with AZA.

Inflamm Bowel Dis. 2010; 16(5): 723-724
Adalimumab for cutaneous metastatic Crohn's disease

Cury DB, Moss AC, Elias G, Nakao A.

No abstract available

Inflamm Bowel Dis. 2010; 16(5): 830-835
Small bowel resection rates in Crohn's disease and the indication for surgery over time: Experience from a large tertiary care center
Lazarev M, Ullman T, Schraut WH, Kip KE, Saul M, Regueiro M.

BACKGROUND: Our primary aim was to determine if the rate of small bowel resection (SBR) has declined over time among Crohn's disease (CD) patients seen at a single academic institution. A secondary aim was to establish whether the indication for surgery has changed. METHODS:: Patients with a primary or secondary ICD-9 code for CD (555.0-555.9) who underwent SBR at the University of Pittsburgh were included. Patients were divided into 4 separate time periods based on when they had surgery: 1995-1998 (Period 1), 1999-2001 (Period 2), 2002-2004 (Period 3), and 2005-2007 (Period 4). Medical records were reviewed for the 6 months preceding surgery. Use of 5-ASAs, immunomodulators (IMs), tumor necrosis factor (TNF) antagonists, and corticosteroids were noted. Disease behavior was defined as nonstricturing, nonpenetrating (B1), stricturing (B2), and penetrating (B3). Proportions of patients undergoing SBR were calculated according to calendar cohort and these rates were examined for time trends. RESULTS:: In all, 227 unique patients were analyzed for a total of 236 surgeries. The rates of 5-ASA, IM, and corticosteroid use were similar across the 4 time periods. By contrast, TNF antagonist usage progressively increased over time (0%, 18%, 34%, 35%; P = 0.0002). The annual rate of SBR per period did not change (1.6%, 1.9%, 1.6%, 1.9%; P = 0.93). Similarly, the disease behavior did not change over time. CONCLUSIONS:: While the frequency of TNF antagonist use in CD at the University of Pittsburgh has increased over time, the rate of SBR and indication for surgery has remained unchanged. These findings may be explained by long-standing, complicated disease refractory to medical therapy.

Inflamm Bowel Dis. 2010; 16(5): 847-855
Relationships between inflammatory bowel disease and perinatal factors: Both maternal and paternal disease are related to preterm birth of offspring
Bengtson MB, Solberg IC, Aamodt G, Jahnsen J, Moum B, Vatn MH; and the IBSEN Study Group.

BACKGROUND:: The aims of this study were to explore the influences of familial, maternal, and paternal inflammatory disease (IBD) on perinatal outcomes in the offspring and the risk for development of IBD related to perinatal factors. METHODS:: Eighty-five patients with Crohn's disease (CD) and 86 with ulcerative colitis (UC) were included from a population-based incidence study enrolled 1990-1994. Family and birth records of these patients, as well as of their 207 infants, were drawn from the Norwegian Medical Birth Registry, established in 1967, and compared with the national birth cohort from the same period. RESULTS:: Maternal (odds ratio [OR] = 2.15, 95% confidence interval [CI]: 1.36, 3.39) and paternal IBD (OR = 3.02, 95% CI: 1.82, 5.01) influenced the risk of preterm birth (<37 weeks), which further increased if the affected parents had a first-degree relative with IBD (OR = 4.29, 95% CI: 1.59, 11.63). Maternal CD was associated with lower birth weight in the offspring (crude difference: 271.79 g, 95% CI: 87.83, 455.77, versus controls). Maternal UC increased the risk of perinatal bacterial infection in the offspring (OR = 6.03, 95% CI: 2.03, 17.91). IBD patients (2.3%) were less likely to be delivered by cesarean section than controls (8.1%) (OR = 0.27, CI: 95%: 0.10, 0.73). CONCLUSIONS:: Familial, maternal, and paternal IBD were linked to preterm birth, which might be explained by genetic mechanisms. The present protective effect of cesarean sections needs further clarification in future studies.

World J Gastroenterol. 2010 Apr 14;16(14):1776-81.
Efficacy of early treatment with infliximab in pediatric Crohn's disease.
Lee JS, Lee JH, Lee JH, Lee HJ, Kim MJ, Lee HJ, Choe YH.

AIM: To investigate the effectiveness of early infliximab use for induction and maintenance therapy in pediatric Crohn's disease. METHODS: We performed a retrospective chart review of 36 patients with Crohn's disease. Ten patients (group A) were treated with mesalamine after induction therapy with oral prednisolone, and 13 patients (group B) were treated with azathioprine after induction therapy with oral

prednisolone. Thirteen patients (group C) received infliximab and azathioprine for induction and maintenance therapy for the first year, and were treated with azathioprine after 1 year. All patients were followed for at least 24 mo. Efficacy was determined by the relapse rate using the pediatric Crohn's disease activity index score in each group at 12 and 24 mo. RESULTS: At the 1 year follow-up, the relapse rate (23.1%, 3 of 13 patients) in group C was lower than that (61.5%, 8 of 13 patients) in group B (P = 0.047). At the 2 years follow-up, the relapse rate (38.5%, 5 of 13 patients) in group C was lower than that (76.9%, 10 of 13 patients) in group B (P = 0.047). Adverse events in group C were fewer than in groups A and B. CONCLUSION: Early induction with infliximab at diagnosis, known as "top-down" therapy, was effective for reducing the relapse rate compared to conventional therapies for at least 2 years.

Digestion. 2010;81(4):237-43. Epub 2010 Jan 29.
Do patients with ulcerative colitis diagnosed at a young age have more severe disease activity than patients diagnosed when older?
Lee JH, Cheon JH, Moon CM, Park JJ, Hong SP, Kim TI, Kim WH.

BACKGROUND/AIMS: To compare the clinical features and disease behavior of ulcerative colitis (UC) according to the age at onset. METHODS: This retrospective study included 455 patients with UC who were diagnosed and treated between 1990 and 2008 at a single tertiary institution in Korea. The patients were divided into 2 groups according to their age at diagnosis of UC: an elderly group (>or=40 years) and a young group (<40 years). Clinical findings at diagnosis, extent of disease, treatment modalities used, cumulative admission rates, cumulative relapse rates, and surgery rates were analyzed according to these age groups. RESULTS: Two hundred and forty-two patients with UC (53.2%) were diagnosed before the age of 40 years. Disease severity at initial presentation as assessed by diarrhea frequency, the presence of pancolitis, and the use of steroids were higher in the young group; however, clinical disease course including cumulative admission rates, cumulative relapse rates, and surgery rates were not significantly different between the 2 groups. CONCLUSIONS: Certain clinical features and the extent of disease in UC patients appear to be more severe when the disease is diagnosed at younger age; however, their disease course and prognosis might not be different from those of their older counterparts.

Expert Opin Drug Saf. 2010 Apr 9. [Epub ahead of print]
Efficacy and safety of drugs for ulcerative colitis.
Rosenberg LN, Peppercorn MA.

Importance of the field: Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon that carries considerable burden and morbidity for patients and presents a constant challenge in management for gastroenterologists. Continued advances in medical therapies provide a range of treatment options for patients, but with this is the need to balance the potential benefits of a particular medication with its side effect profile in both the short and the long term. Areas covered in this review: This article will review the current drugs used in the treatment of UC, including 5-amninosalicylates, antibiotics, steroids, immunomodulators and biologics, with particular attention to their indications, efficacy and toxicity profile. What the reader will gain: The reader will gain a comprehensive understanding of the various medical therapies used in the treatment of UC with focus on efficacy and toxicity profiles, allowing providers to choose appropriate medical therapies for their patients. Take home message: The particular agent used depends upon the extent and severity of disease, with mild-to-moderate disease treated with conventional therapy including 5-amninosalicylates. Steroids are used in the short term to bring active disease into remission, and the more aggressive immunomodulators and biologics are reserved for more severe disease given their toxicity profiles.

Med J Aust. 2010 Apr 5;192(7):375-7.
Anti-tumour necrosis factor-alpha treatment for perianal Crohn's disease in Australia.
Burger DC, Lawrance IC, Bampton PA, Prosser R, Croft A, Gilshenan K, Radford-Smith GL, Florin TH.

OBJECTIVE: To examine the prevalence of perianal Crohn's disease (PCD) and the eligibility of PCD patients to access anti-tumour necrosis factor-alpha (anti-TNFalpha) treatment under current Australian Pharmaceutical Benefits Scheme (PBS) guidelines. DESIGN, SETTING AND PARTICIPANTS: A retrospective study of patients with Crohn's disease (CD) and PCD attending four large adult inflammatory bowel disease (IBD) centres in Australia between January 2004 and May 2008. Patients for

whom anti-TNFalpha therapy was clinically indicated were assessed to determine whether they satisfied PBS criteria for subsidised medication. MAIN OUTCOME MEASURES: Prevalence of CD and PCD in patients attending different IBD centres; eligibility of PCD patients for PBS-subsidised anti-TNFalpha medication. RESULTS: Data were available on 3589 patients, representing about 6% of all patients with IBD in Australia. Of the 1815 patients with CD, 310 (17%) had PCD. Anti-TNFalpha therapy was deemed clinically indicated for 166 patients with PCD (54%), of whom 49 (30%) did not qualify for PBS-funded therapy. CONCLUSION: Thirty per cent of patients with clinically significant PCD currently do not have access to PBS-subsidised optimal medical treatment. We believe that PBS criteria should be extended to include this subgroup of IBD patients.

World J Gastroenterol. 2010 Apr 21;16(15):1924-7.
Cystic fibrosis and Crohn's disease: successful treatment and long term remission with infliximab
Vincenzi F, Bizzarri B, Ghiselli A, de' Angelis N, Fornaroli F, de' Angelis GL.

The association of cystic fibrosis and Crohn's disease (CD) is well known, but to date, there are very few cases in the literature of patients suffering from mucoviscidosis who have required treatment with infliximab. We report the case of a 23-year-old patient suffering from cystic fibrosis and severe CD treated successfully with infliximab without any infective complications or worsening of the pulmonary disease and with a long term (2 years) complete remission.

Medical Decision Making 2010; 30(1):132-142 (epub 15 july 2009)
A Maximum Likelihood Estimator of a Markov Model for Disease Activity in Crohn s Disease and Ulcerative Colitis for Annually Aggregated Partial Observations
Borg, Sixten; Persson, Ulf; Jess, Tine; Thomsen, Ole stergaard; Ljung, Tryggve; Riis, Lene; Munkholm, Pia

No abstract available

Nat Rev Gastroenterol Hepatol. 2010 Feb;7(2):79-85.
The potential for disease modification in Crohn's disease.
Van Assche G, Vermeire S, Rutgeerts P.

The natural history of Crohn's disease is characterized by progression to complicated and disabling disease, often necessitating surgical interventions. There is either circumstantial or direct evidence to support the disease-modifying potential of several therapeutic agents. Healing of endoscopic lesions is an emerging surrogate marker of disease modification, as mucosal lesions are considered to reflect ongoing inflammation and tissue damage that lead to the formation of fistulas and fibrotic strictures, which are the main indications for surgery. In contrast to systemic steroids, both azathioprine and anti-tumor necrosis factor (TNF) agents have demonstrated the potential of mucosal healing. Prevention of hospitalization and surgery in the short and medium term has been demonstrated for the anti-TNF agents infliximab and adalimumab. The evidence supporting a role for medical therapy in the prevention of fibrotic wall thickening and in the obliteration of fistula tracks is limited and should be the focus of further prospective studies. These studies should validate predictors of complicated disease and randomized studies should be performed in high-risk groups to investigate whether early introduction of immunosuppressive agents or biologic therapies slows down disease progression and alters the natural history of the disease.

J Gastroenterol Hepatol 2010; 25(5): 886-891
Efficacy and safety of infliximab as rescue therapy for ulcerative colitis refractory to tacrolimus
Shuji Yamamoto, Hiroshi Nakase, Minoru Matsuura, Yusuke Honzawa, Satohiro Masuda, Ken-ichi Inui, Tsutomu Chiba

No abstract available

Safety

Semin Arthritis Rheum. 2010 Apr;39(5):327-46. Epub 2008 Dec 31.
The risk of infections with biologic therapies for rheumatoid arthritis
Furst DE.

OBJECTIVES: To assess the risk of serious and nonserious bacterial and viral infections associated with the use of biologic therapy (abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab) in patients with rheumatoid arthritis (RA). METHODS: Information was derived from PubMed, EMBASE, and the Cochrane clinical trials register and database of systematic reviews and relevant congress abstracts up to and including February 2008. RESULTS: Compared with the general population, patients with RA have a heightened risk of infection, including tuberculosis. Long-term clinical trials and postmarketing studies indicate that anakinra and the tumor necrosis factor (TNF) inhibitors are associated with an increased risk of infections versus conventional disease-modifying antirheumatic drugs (DMARDs), especially early in the course of treatment. The most common sites of infection are the respiratory tract (including pneumonia), skin and soft tissue, and the urinary tract. The risk of tuberculosis also appears higher with TNF inhibitors (in particular, infliximab) versus DMARDs, although this can be reduced by screening and prophylaxis. TNF inhibitors do not appear to significantly increase the risk of reactivating chronic viral infections. Influenza and pneumococcal vaccinations are generally effective in the face of TNF inhibitors or abatacept. Available data suggest that the risk of infections and serious infections with abatacept and rituximab may be similar to that of the TNF inhibitors. To date, there have been no reports from clinical trials of increased tuberculosis or opportunistic infections with abatacept or rituximab. CONCLUSIONS: All marketed TNF inhibitors for compared to control RA appear to increase the risk of serious and nonserious infections compared with DMARDs. Although suggestive, data for abatacept and rituximab are less definitive and longer periods of patient exposure to these agents are needed before an assessment of their risks can be made.

Aliment Pharmacol Ther 2010 Feb 16. [Epub ahead of print]
Review article: clinically significant liver injury in patients treated with natalizumab
Bezabeh S, Flowers CM, Kortepeter C, Avigan M.

Background: Natalizumab (Tysabri) is a recombinant monoclonal antibody approved for the treatment of patients with multiple sclerosis (MS) and patients with Crohn's disease (CD). Because of its immunosuppressive effects, natalizumab has been associated with a number of atypical and opportunistic infections. Methods The FDA maintains a database of adverse event reports (AERS). We searched the AERS database for reports of serious liver injury associated with natalizumab use from November 2004, when the drug was approved, through June 30, 2008. Results: The search resulted in six spontaneously reported postmarketing cases of severe drug-induced liver injury. Four of six patients developed liver injury with elevations of serum transaminases and hyperbilirubinemia after only a single infusion of natalizumab. One of these patients experienced repeated increases of aminotransferases and bilirubin when natalizumab was re-administered. Conclusions: Serious hepatic injury may occur in association with natalizumab use. Health professionals should be alerted to possible serious liver injury in patients receiving natalizumab.

Am J Med. 2010 Apr;123(4):350-7.
Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis.
Kimball AB, Guerin A, Latremouille-Viau D, Yu AP, Gupta S, Bao Y, Mulani P.

BACKGROUND: Past studies suggest an association between psoriasis and the risk of developing coronary heart disease. The objectives of this study were to estimate the 10-year risks of coronary heart disease and stroke in patients with moderate to severe psoriasis, to compare risks between patients and the general population, and to determine whether risk profiles are affected by disease severity. METHODS: Data were pooled from patients with moderate to severe psoriasis (Psoriasis Area and Severity Index [PASI] score> or =10) who were enrolled in Phase II (M02-528) or Phase III trials (Comparative Study of HUMIRA vs Methotrexate vs Placebo In PsOriasis PatieNts[CHAMPION], Randomized Controlled EValuation of Adalimumab Every Other Week Dosing in Moderate to Severe Psoriasis TriAL[REVEAL]) evaluating adalimumab. Risks of coronary heart disease and stroke were estimated using the Framingham risk score algorithm and a stroke risk function based on the Framingham Heart Study cohorts. To compare risks between patients with psoriasis and the general

population, average population risks were imputed on the basis of age and gender. Wilcoxon rank-sum tests evaluated risk differences between patients with psoriasis and the general population and between patients with moderate psoriasis and patients with severe psoriasis. RESULTS: A total of 1591 patients were identified, including 1082 patients with PASI scores> or =10 and < or = 20 and 509 patients with PASI scores>20. Patients with PASI scores from 10 to 20 and PASI scores>20 had similar 10-year risks of coronary heart disease (12.3% and 12.2%; P=.49) and stroke (8.3% and 8.7%; P=.28). Compared with the general population, 10-year risks of patients with psoriasis were 28% greater for coronary heart disease (P<.001) and 11.8% greater for stroke (P=.02). CONCLUSION: Patients with moderate to severe psoriasis had increased risks of coronary heart disease and stroke compared with the general population.

J Cutan Med Surg. 2009 Dec;13 Suppl 3:S139-47.
Update on alefacept safety
Wexler D, Searles G, Landells I, Shear NH, Bissonnette R, Papp K, Poulin Y, Langley R, Gulliver WP.

BACKGROUND: Alefacept has been demonstrated in clinical trials to be an effective, safe, and well-tolerated treatment strategy when used alone or in combination with other antipsoriatic therapies in patients with chronic plaque psoriasis. OBJECTIVE: AWARE (Amevive Wisdom Acquired from Real-World Evidence) is a multicenter, observational, Canadian phase IV registry evaluating the efficacy and safety of alefacept, alone or in combination with other antipsoriatic therapies, in patients with psoriasis. METHODS: Patients with chronic plaque psoriasis were treated with at least one course of alefacept followed by an off-treatment period, typically lasting 12 or more weeks. Prospective follow-up was at least 60 weeks, depending on when patients presented for retreatment. Safety data collected throughout the study included the incidence of serious adverse events (SAEs), dosing suspensions, and withdrawals owing to adverse events. RESULTS: Twelve SAEs were reported in psoriasis patients treated with at least one course of alefacept, with only one considered to be possibly related to the study drug. Approximately one-quarter of patients missed at least one dose of alefacept during the course of the study. A total of 291 doses of alefacept were missed, representing almost 4% of the total doses administered in this group of patients. Low CD4(+) count was the most frequent reason for missed doses; however, no patient had persistently low CD4(+) counts requiring permanent discontinuation of alefacept treatment. Seven patients in the AWARE registry discontinued treatment with alefacept, with the most common reason being patient request. CONCLUSION: The AWARE study supports the safety of alefacept used alone or in combination with other antipsoriatic therapies, in a broad population of real-world chronic plaque psoriasis patients in Canada.

Med Oncol. 2010 Apr 7. [Epub ahead of print]
Golimumab and malignancies: true or false association?
Zidi I, Bouaziz A, Mnif W, Bartegi A, Ben Amor N.

Malignancy is one of the comorbidities linked to golimumab, a biological TNF-alpha blocker. In this systematic review and meta-analysis, we searched different databases and analyzed original publications to elucidate the remaining open question about the real association of malignancies with golimumab therapy. The most frequent cancer in patients treated with golimumab, in association or not with methotrexate, is the lung adenocarcinoma. However, lymphoma is not very commonly represented in these patients. We show that there is no major and evident risk of malignancies associated with golimumab in current scientific literature. An increased risk of malignancies may be associated with golimumab, but this warrants further clinical confirmation. Also, this risk mentioned in different studies must be taken with caution because of number of limits and biases.

Expert Opin Drug Saf. 2010 Apr 2. [Epub ahead of print]
A safety assessment of tumor necrosis factor antagonists during pregnancy.
Osting VC, Carter JD.

Importance of the field: Disease modifying antirheumatic drugs are being increasingly utilized in the treatment of many autoimmune disorders. TNF-alpha antagonists have become the standard of care in treating many of these autoimmune diseases. Because these autoimmune disorders often affect women in their childbearing years, the safety of anti-TNF therapy in pregnancy becomes important. Areas covered in this review: We critically review the current literature on anti-TNF therapy safety in pregnancy. The available data regarding the anti-TNFs in the setting of pregnancy from 1999 to the present are

reviewed. What the reader will gain: Case reports and small case series have produced conflicting results, yet their results should only be viewed with cautious interest. Two database reviews suggest little to no risk of congenital anomalies, whereas a much larger independent review of the FDA database reveals congenital anomalies born to mothers who were exposed to anti-TNFs during pregnancy. An ongoing prospective registry (Organization of Teratology Information Services) suggests that about 7 - 10% of children born to mothers taking a TNF antagonist during pregnancy are born with congenital anomalies. Take home message: Whether or not these data represent a significant increase, or if a definitive pattern of birth defects exists, remains in question. All these sources have limitations, which are discussed. Further studies are needed to definitively determine the safety and role of anti-TNFs in pregnancy.

J Rheumatol. 2010 Apr 1. [Epub ahead of print]
Observational Studies of Infections in Rheumatoid Arthritis: A Metaanalysis of Tumor Necrosis Factor Antagonists
Bernatsky S, Habel Y, Rahme E.

OBJECTIVE: Published metaanalyses of tumor necrosis factor (TNF) antagonists and infection have focused on randomized controlled trials, which tend to have short duration, relatively small size, and stringent inclusion/exclusion criteria that may limit enrollment to patients at low risk of infection. We performed a systematic review and synthesis of observational studies of TNF antagonists and infection risk. METHODS: We conducted a systematic literature search of studies estimating overall risk of serious infection after anti-TNF exposure in rheumatoid arthritis (RA). We estimated a pooled relative risk (RR) for the relevant observational studies, using a random-effects model. RESULTS: Five cohort studies and 2 nested case-control studies were included in the metaanalysis. Anti-TNF therapy appeared to significantly increase risk of serious infection (pooled adjusted RR 1.37, 95% CI 1.18, 1.60). CONCLUSION: Our metaanalysis of observational data demonstrated an increased risk of serious infection in subjects with RA receiving anti-TNF therapy, versus those not receiving these agents.

Clin Exp Dermatol. 2010 Mar 19. [Epub ahead of print]
Multiple cutaneous malignancies arising in a patient with Crohn disease treated with concomitant azathioprine and antitumour necrosis factor-alpha
Fogo AJ, Hunt JB, Clement M.

No abstract available

Inflamm Bowel Dis. 2010; 16(5): 881-895
Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding
Gisbert JP.

The aim of this article is to critically review available data regarding the safety of immunomodulators and biological therapies during pregnancy and breast-feeding in women with inflammatory bowel disease. Methotrexate and thalidomide can cause congenital anomalies and are contraindicated during pregnancy (and breast-feeding). Although thiopurines have a Food and Drug Administration (FDA) rating D, available data suggest that these drugs are safe and well tolerated during pregnancy. Although traditionally women receiving azathioprine or mercaptopurine have been discouraged from breast-feeding because of theoretical potential risks, it seems that these drugs may be safe in this scenario. Treatment with cyclosporine for steroid-refractory ulcerative colitis (UC) during pregnancy can be considered safe and effective, and the use of this drug should be considered in cases of severe UC as a means of avoiding urgent surgery. Breast-feeding is contraindicated for patients receiving cyclosporine. Biological therapies appear to be safe in pregnancy, as no increased risk of malformations has been demonstrated. Therefore, the limited clinical results available suggest that the benefits of infliximab and adalimumab in attaining response and maintaining remission in pregnant patients might outweigh the theoretical risks of drug exposure to the fetus. Stopping therapy in the third trimester may be considered, as it seems that transplacental transfer of infliximab is low prior to this. Certolizumab differs from infliximab and adalimumab in that it is a Fab fragment of an antitumor necrosis factor alpha monoclonal antibody, and therefore it may not be necessary to stop certolizumab in the third trimester. The use of infliximab is probably compatible with breast-feeding.

Nat Rev Gastroenterol Hepatol. 2010 Apr;7(4):231-5.
Disseminated coccidioidomycosis in a patient managed with adalimumab for Crohn's disease.
Mitter SS, Derhovanessian A, Hillman JD, Uslan DZ.

BACKGROUND: A 50-year-old man presented with a 2-3 month history of left lower quadrant abdominal pain, right periorbital headache, blurry vision, tinnitus, polydipsia, right elbow pain, and a 32 kg weight loss over the past year. He had a 34-year history of complicated Crohn's disease that was notable for surgical stricture repair and partial colectomy for bowel perforation. The patient was receiving mesalazine and 6-mercaptopurine and, 2 months before admission, had stopped a 4-month therapy course with the biologic agent adalimumab for treatment of Crohn's disease. INVESTIGATIONS: Physical examination, brain and elbow MRI scans, chest CT scan, routine blood analyses, assessment of coccidioidomycosis antibody levels, immunodiffusion and complement fixation studies in serum and cerebrospinal fluid, full-body technetium-99m nuclear bone scan, hematoxylin and eosin staining of resected tissue specimens. DIAGNOSIS: Disseminated coccidioidomycosis with meningeal, bone, soft tissue and pulmonary involvement. MANAGEMENT: The patient underwent treatment with amphotericin B liposomal complex and oral fluconazole and right elbow surgical debridement and irrigation. All immunosuppressive therapy was stopped.

J Am Acad Dermatol. 2010 May;62(5):874-9. Epub 2009 Nov 13.
Erythema multiforme during anti-tumor necrosis factor treatment for plaque psoriasis.
Ahdout J, Haley JC, Chiu MW.

Tumor necrosis factor alpha (TNF-alpha) inhibitors constitute a class of biologic treatments utilized in the management of psoriasis. We report a case of a patient treated for chronic plaque psoriasis with the anti-TNF-alpha monoclonal antibody adalimumab, who developed erythema multiforme (EM). The patient had previously developed EM on two occasions while taking the TNF-alpha inhibitor etanercept. EM has previously been reported in connection with other TNF-alpha inhibitors, including etanercept and infliximab. To our knowledge, this is the first case reported in the literature documenting EM occurring subsequent to adalimumab treatment for psoriasis. The recurrent development of EM in our patient while being treated with distinct TNF-alpha inhibitors may suggest that EM is the consequence of a class effect with TNF-alpha inhibitors.

Rheumatology (Oxford). 2010 May;49(5):891-7. Epub 2010 Feb 23.
Heterophile interference accounts for method-specific dsDNA antibodies in patients receiving anti-TNF treatment.
Alshekaili J, Li C, Cook MC.

OBJECTIVE: To evaluate analytical explanations for the highly reported incidence of antibodies to dsDNA in patients receiving TNF antagonists. METHODS: Sixty serum samples from patients receiving biological anti-TNF medication were assessed for the presence of dsDNA antibodies using three standard diagnostic platforms [ELISA, IIF and multiplex bead array (MBA)], before and after treatment to block heterophile antibodies. Results were compared with those obtained using serum samples from patients with SLE. RESULTS: We identified significant method-specific discrepancies in the estimation of dsDNA antibodies in patients receiving TNF antagonists. dsDNA antibodies were frequent according to ELISA and IIF, but rare according to MBA. Blockade of heterophile antibodies resulted in a significant reduction in titres of dsDNA antibodies detected by IIF. In contrast, there was a much greater consistency for dsDNA antibody results in SLE, especially for those present in high titre, and blockade of heterophile antibodies did not result in a change between the two paired samples by IIF or MBA. CONCLUSION: There is a significant method-specific variation in the detection of dsDNA antibodies in patients receiving TNF antagonists, due in part to the effects of heterophile antibodies.

Rheumatology 2010 49: 1021-1022
Alfonso Massara, Luigi Cavazzini, Renato La Corte, and Francesco Trotta. **Comment on: Sarcoid-like granulomatosis in patients treated with tumour necrosis factor blockers: 10 cases** - Rheumatology 2010 49: 1019-1021. **And the reply by Claire Immediato Daïen, Cédric Lukas, Bernard Combe, and Jacques Morel. Comment on: Sarcoid-like granulomatosis in patients treated with tumour necrosis factor blockers:** 10 cases: reply.

No abstract available

Alimentary Pharmacology & Therapeutics 2010; 31(10): 1152-1153
Infliximab safety profile and long-term applicability in inflammatory bowel disease: clinical experiences from the Eastern side of Europe
T. MolnÁr, K. Farkas, F. Nagy, Z. Szepes, T. Wittmann

No abstract available

Clin Gastroenterol Hepatol. 2010 May;8(5):475-6. Epub 2010 Jan 6.
Adalimumab level in breast milk of a nursing mother.
Ben-Horin S, Yavzori M, Katz L, Picard O, Fudim E, Chowers Y, Lang A.

No abstract available

Drugs Today (Barc). 2010 Feb;46(2):119-36.
Efficacy and safety of biologicals against immune-mediated diseases: do benefits outweigh risks?
Korkina L, Trakhtman P, De Luca C, Leoni L, Raskovic D, Pastore S.

The success of molecular biology in identifying molecular pathways underlying chronic immune-mediated diseases and the rapid development of gene/cell engineering biotechnologies has resulted in the development of a number of targeted biological drugs, which have revolutionized the therapy of these diseases. Numerous data published over the last 10-15 years demonstrate a dramatic improvement in the clinical efficacy of biologics compared with conventional drugs. However, professional and public concern about serious biological drug-associated adverse events has also been growing steadily. We critically analyze recent literature on the efficacy and safety of biologics in the management of rheumatoid arthritis, psoriasis, psoriatic arthritis and immune thrombocytopenia. Our analysis of benefits, resistance to the therapy, risk of infections, tumors and other serious complications related to chronic administration of biologics is based on the molecular/cellular mechanisms of their interaction with the immune system. We also address whether it is feasible to attenuate the risks associated with biologics without limiting their benefits.

Expert Opin Drug Saf. 2010 May;9(3):421-9.
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Osting VC, Carter JD.

IMPORTANCE OF THE FIELD: Disease modifying antirheumatic drugs are being increasingly utilized in the treatment of many autoimmune disorders. TNF-alpha antagonists have become the standard of care in treating many of these autoimmune diseases. Because these autoimmune disorders often affect women in their childbearing years, the safety of anti-TNF therapy in pregnancy becomes important. AREAS COVERED IN THIS REVIEW: We critically review the current literature on anti-TNF therapy safety in pregnancy. The available data regarding the anti-TNFs in the setting of pregnancy from 1999 to the present are reviewed. WHAT THE READER WILL GAIN: Case reports and small case series have produced conflicting results, yet their results should only be viewed with cautious interest. Two database reviews suggest little to no risk of congenital anomalies, whereas a much larger independent review of the FDA database reveals congenital anomalies born to mothers who were exposed to anti-TNFs during pregnancy. An ongoing prospective registry (Organization of Teratology Information Services) suggests that about 7 - 10% of children born to mothers taking a TNF antagonist during pregnancy are born with congenital anomalies. TAKE HOME MESSAGE: Whether or not these data represent a significant increase, or if a definitive pattern of birth defects exists, remains in question. All these sources have

limitations, which are discussed. Further studies are needed to definitively determine the safety and role of anti-TNFs in pregnancy.

Ann Rheum Dis. 2010 May;69(5):817-21. Epub 2009 Jul 5.
Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study.
Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, Dijkmans BA, Tak PP, Wolbink GJ.

OBJECTIVE: To investigate how antibodies against anti-tumour necrosis factor (anti-TNF) agents influence response after switching from infliximab to adalimumab in rheumatoid arthritis (RA). METHODS: This cohort study consisted of 235 patients with RA, all treated with adalimumab. At baseline 52 patients (22%) had been previously treated with infliximab ('switchers'), and 183 (78%) were anti-TNF naive. Disease activity (using the 28-joint count Disease Activity Score (DAS28)) and presence of antibodies against infliximab and adalimumab were assessed. Clinical response to adalimumab was compared between switchers and anti-TNF naive patients and their anti-infliximab and anti-adalimumab antibody status. RESULTS: After 28 weeks of adalimumab treatment the decrease in DAS28 (Delta DAS28) for the 235 patients was 1.6+/-1.5 (mean+/-SD). Anti-adalimumab antibodies were detected in 46 patients (20%). Delta DAS28 was 1.8+/-1.4 in patients without anti-adalimumab and 0.6+/-1.3 in patients with anti-adalimumab ($p<0.0001$). Thirty-three of the 52 switchers (63%) had anti-infliximab antibodies. Patients with anti-infliximab more often developed anti-adalimumab than anti-TNF naive patients (11 (33%) vs 32 (18%); $p=0.039$). Delta DAS28 was greater for anti-TNF naive patients (1.7+/-1.5) than for switchers without anti-infliximab antibodies (Delta DAS28=0.9+/-1.4) ($p=0.009$). Delta DAS28 for switchers with anti-infliximab was 1.2+/-1.3 and did not differ significantly from anti-TNF naive patients ($p=0.262$). CONCLUSION: Switchers with anti-infliximab antibodies more often develop antibodies against adalimumab than anti-TNF naive patients. Response to adalimumab was limited in switchers without anti-infliximab antibodies, which raises the question whether a second anti-TNF treatment should be offered to patients with RA for whom an initial treatment with an anti-TNF blocker fails, in the absence of anti-biological antibodies.

Rheumatology (Oxford). 2010 Apr 19. [Epub ahead of print]
Onset of Wegener's granulomatosis during therapy with golimumab for rheumatoid arthritis: a rare adverse event?
Parekh K, Ching D, Rahman MU, Stamp LK.
No abstract available

Arthritis Res Ther. 2010 Apr 14;12(2):R67. [Epub ahead of print]
Infections requiring hospitalization in the Abatacept clinical development program: an epidemiological assessment.
Simon TA, Askling J, Lacaille D, Franklin J, Wolfe F, Covucci A, Suissa S, Hochberg MC.

ABSTRACT: INTRODUCTION: Patients with rheumatoid arthritis (RA) have an increased risk of infection and this risk appears to be higher with anti-TNF agents. We pooled data from the cumulative abatacept RA clinical development program, both double-blind and open-label periods, to estimate the incidence rates (IRs) of infections requiring hospitalization including pneumonia and opportunistic infections, in comparison with RA patients treated with non-biologic DMARDs from several reference cohorts. METHODS: Infections reported in 7 abatacept clinical trials of RA patients (double-blind and open-label periods) were tabulated. Comparisons were made between the observed IRs in abatacept-treated patients and those in over 133,000 patients exposed to non-biologic DMARDs in 6 reference RA cohorts. Age- and sex-adjusted IRs of infections requiring hospitalization, including pneumonia (most frequent hospital infection), were used to estimate the expected IRs with abatacept by the method of indirect adjustment. Standardized incidence ratios (SIR) and 95% CI were calculated comparing incidence in the cumulative abatacept experience with incidence in each RA cohort. RESULTS: A total of 1955 (double-blind period) and 4134 (double-blind + open-label periods with a cumulative exposure of 8392 person-years) abatacept-treated RA patients were analyzed. Observed IRs for infections requiring hospitalization during the double-blind period were 3.05 per 100-patient years for abatacept-treated patients and 2.15 per 100 patient years for placebo. In the cumulative population, observed IR for infections requiring hospitalization was 2.72 per 100-patient years. Rates for abatacept were similar to expected IRs based

on other RA non-biologic DMARD cohorts. CONCLUSIONS: IRs of infections requiring hospitalization and pneumonia in abatacept trials are consistent with expected IRs based on reference RA DMARD cohorts. RA patients are at higher risk of infection compared with the general population, making the RA DMARD cohorts an appropriate reference group. The safety of abatacept, including incidence of infections requiring hospitalization, will continue to be monitored in a post-marketing surveillance program.

Ann N Y Acad Sci. 2010 Apr;1193(1):153-9.
Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-alpha therapy.
Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Llorca J.

Increased prevalence of insulin resistance has been observed in patients with rheumatoid arthritis (RA). High-grade systemic inflammation is implicated in the development of insulin resistance in these patients. Tumor necrosis factor (TNF)-alpha is a potent proinflammatory cytokine that plays a role in the initiation and progression of inflammation and the mechanisms associated with accelerated atherosclerosis in RA. In assessing data immediately prior to and after intravenous infusion of the anti-TNF-alpha monoclonal antibody-infliximab in RA patients on period treatment with this drug attributable to disease refractory to conventional disease-modifying antirheumatic drugs, a dramatic improvement of insulin resistance and insulin sensitivity was observed. A long-term positive effect of TNF-alpha antagonists infliximab and etanercept on insulin resistance in RA patients with severe disease was also reported. These results highlight the importance of therapies that act blocking TNF-alpha function to reduce the mechanisms implicated in the development of the metabolic syndrome observed in RA.